(α-Nitroalkyl)-*ONN*-azoxysulfones and some of their transformations

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A regioselective method for the synthesis of [(α-nitroalkyl)-*ONN*-azoxy]alkyl- and -arylsulfones by oxidative condensation of pseudonitroles with aliphatic and aromatic sulfamides under the action of dibromoisocyanurate (DBI) was proposed. The behavior of the azoxysulfones obtained toward acids and bases as well as futher transformations of the products of acid hydrolysis into salts and halo-derivatives of nitroalkylazoxysulfones were investigated.

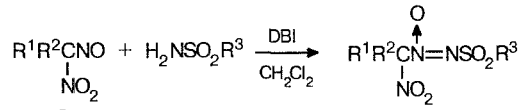
Key words: nitroalkylazoxysulfones; dehydroxymethylation; halogenation.

Until now no nitroalkylazoxysulfones of the general formula $R^1R^2C(NO_2)N(O)=NSO_2R^3$ (**1**) (R^1, R^2 = Alk, H; R^3 = Alk, Ar) have been known. However, they are of interest as potentially biologically active compounds, like those in which the azoxy moiety is bonded to heteroatoms (*e.g.*, to nitrogen[1] or phosphorus[2]).

The most general method for the synthesis of diazene oxides is the interaction of nitroso compounds with amino-derivatives in the presence of oxidants, most often dibromoisocyanurate (DBI) (*e.g.*, see the review[3]).

In particular, reactions of pseudonitroles with cyanamide[4] and with amides of phosphoric and phosphonic acids[2] have been carried out.

We found that treatment of pseudonitroles (**2**) with amides of aliphatic or aromatic sulfonic acids (**3**) in the presence of DBI readily gives azoxysulfones **1** in high yields.



2 **3** **1a–g**

$R^1 + R^2 = CH_2OCMe_2OCH_2$

a: R^3 = Me; **b**: R^3 = Ph; **c**: R^3 = Et

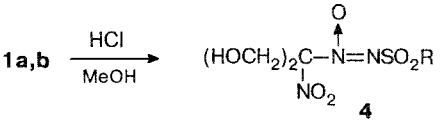
d: $R^1 + R^2 = CH_2OCHMeOCH_2$, $R^3 = (p\text{-}MeC_6H_4)$

$R^1 = R^2$ = Me

e: R^3 = Me; **f**: R^3 = Et; **g**: R^3 = Ph

The reaction proceeds regioselectively at ~20 °C in inert solvents (CH_2Cl_2, $CHCl_3$) when excess sulfamide is present. The nitroazoxysulfones **1** obtained are stable crystalline or oily compounds. Their structures were elucidated from spectroscopic and elemental analysis data.

The sulfonylazoxynitroalkyl moiety in compounds **1** is stable toward the action of acids and bases. This permits various transformations, not involving this moiety, to be carried out. For example, when solutions of compounds **1a–d** in methanol are treated with hydrogen chloride, the 1,3-dioxane ring is easily opened, which results in the corresponding diols of the azoxysulfonic series (**4**).



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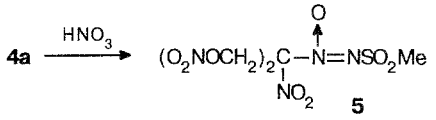
a: R = Me; **b**: R = Ph

The high stability of compounds **4** in acidic media makes it possible to obtain dinitrates (**5**) even when the diols are boiled in 70 % HNO_3.



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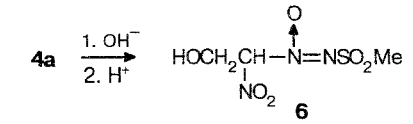
Azoxysulfones **4** have properties typical of β-nitroalcohols.[5] In particular, compound **4a** undergoes dehydroxymethylation in an alkaline medium, which results in nitroalcohol (**6**) after acidification of the reaction mixture.



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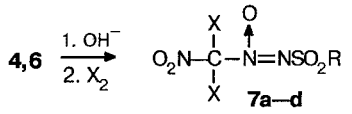
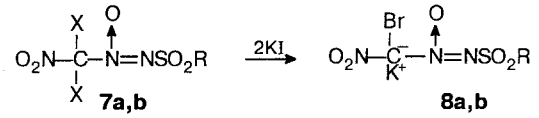
Treatment of compounds **4** or **6** with halogens in an alkaline medium results in the replacement of the hydroxymethyl groups to give (dihalonitromethyl)azoxysulfones (**7**).



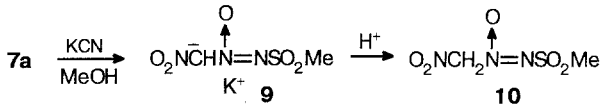
a: R = Me, X = Br **c**: R = Me, X = Cl
b: R = Ph, X = Br **d**: R = Ph, X = Cl

Compounds **4**—**7** are analogous to *gem*-dinitro compounds due to the presence of geminal nitro and sulfonylazoxy groups. For example, they can undergo reduction similarly to dihalodinitromethanes[6] with elimination of one Br atom when treated with KI to give salts (**8**).



a: R = Me; **b**: R = Ph

Treatment with KCN makes it possible to eliminate both bromine atoms to give salt **9**, which is transformed upon acidification into free mesyl-*NNO*-azoxynitromethane (**10**).



Salts **8** and **9** undergo halogenation to give the original dihalides **7**, which is an additional confirmation of the structure of these compounds.

Acidification of compound **8** with sulfuric acid and alkylation of compound **9** with methyl iodide result in complex mixtures, probably due to the decomposition of the reaction products.

Experimental

^{1}H NMR spectra were recorded on Tesla BS-467, Bruker WM-250, and Bruker AM-300 spectrometers (working frequencies 60, 250, and 300 MHz, respectively) using HMDS as the internal standard. ^{13}C NMR (75.5 MHz) and ^{14}N NMR (21.7 MHz) spectra were obtained on a Bruker AM-300 spectrometer. The chemical shifts in the ^{14}N NMR spectra are given relative to $MeNO_2$ as the external standard (δ 0.0) without corrections for the magnetic susceptibility. IR spectra were obtained on UR-20 and Specord IR spectrophotometers in KBr pellets for crystalline compounds and without solvent for liquid compounds. Column chromatography and TLC were performed on Silpearl silica gel (with a luminophore in the case of TLC). Melting points were determined on a Kofler hot stage. DBI were obtained according to the procedure reported previously.[7] The physicochemical parameters and IR spectroscopic data for the compounds obtained are presented in Table 1. The ^{1}H, ^{13}C, and ^{14}N NMR data are given in Tables 2 and 3.

General procedure for the synthesis of azoxysulfones 1a—g. A mixture of pseudonitrole **2** (10 mmol), sulfamide **3** (15 mmol), and DBI (15 mmol) in dry CH_2Cl_2 (50 mL) was stirred at ~20 °C for 0.5—1.5 h (until the appearance of a typical bright-red coloring, TLC monitoring) and filtered. Compounds **1** were isolated from the filtrate by TLC (benzene—ethyl acetate, 2 : 1 as the solvent system). **1a**. Found (%): C, 29.66; H, 4.69; N, 14.09; S, 11.93. $C_7H_{13}N_3O_7S$. Calculated (%): C, 29.68; H, 4.59; N, 14.84; S, 11.31.

Table 1. Physicochemical parameters and IR spectra of the compounds obtained

Compound	Yield (%)	M.p./°C (solvent)	IR, ν/cm^{-1}		
			NO_2	=N→O	SO_2
1a	100	76—78 (hexane—$CHCl_3$)	1580, 1350	1500, 1450	1370, 1150
1b	100	103—106 (hexane—$CHCl_3$)	1580, 1350	1500, 1450	1380, 1170
1c	85	97—99 (hexane—$CHCl_3$)	1575, 1340	1505, 1455	1380, 1150
1d	70	121.5—124.0 (hexane—$CHCl_3$)	1575, 1340	1505, 1455	1380, 1150
1e	100	51 (hexane—$CHCl_3$)	1570, 1340	1500, 1450	1380, 1150
1f	80	Oil	1580, 1350	1505, 1450	1380, 1150
1g	100	108—110 (hexane—$CHCl_3$)	1590, 1360	1500, 1450	1380, 1155
4a	100	Oil	1565, 1340	1500	1155
4b	100	156.5—159.0 ($CHCl_3$—ethyl acetate)	1565, 1350	1500	1385, 1160
5	35	Oil	1595, 1435	1500, 1455	1170
6	70	Oil	1580, 1365	1495, 1440	1365, 1180
7a	75	74—76 (hexane—$CHCl_3$)	1600, 1320	1505	1360
7b	100	66.0—67.5 (hexane—$CHCl_3$)	1595, 1370	1500, 1450	1370, 1170
7c	100	19—21 (hexane)	1605, 1320	1510	1320, 1165
7d	100	27—29 (hexane)	1610, 1370	1515, 1450	1175
8a	95	>350	1600, 1340	1510, 1430	1380, 1190
8b*	45	>350	—	—	—
10	80	102—104 (EtOH)	1580, 1345	1500, 1455	1345, 1160

* UV spectrum (in water), λ/nm: 248, 409.

Table 2. ^{1}H NMR spectra of the compounds obtained

Compound	Solvent	CH_2O	Me	Me(R^3)	Ph	Others
1a	$(CD_3)_2CO$	4.75 s	1.38 s	3.27 s	—	—
1b	$CDCl_3$	4.63 s	1.33 d	—	8.05—7.50 m	
1c	$(CD_3)_2CO$	4.90 s	1.50 s	1.40 t	—	3.5 (q, CH_2)
1d	$CDCl_3$	5.03 d; 4.37 d	1.3 d	2.48 s	7.67 q	4.82 (q, OCHO)
1e	$(CD_3)_2CO$	—	2.27 s	3.33 s	—	—
1f	$CDCl_3$	—	2.16 s	1.37 t	—	3.33 (q, CH_2)
1g	$CDCl_3$	—	2.10 s	—	8.10—7.30 m	—
4a	$(CD_3)_2CO$	4.48 d	—	3.27 s	—	5.32 (t, OH)
4b	$(CD_3)_2CO$	4.40 d	—	—	8.05—7.50 m	5.55 (t, OH)
5	$(CD_3)_2CO$	5.87 d	—	3.43 s	—	—
6	$(CD_3)_2CO$	4.50 d	—	3.30 s	—	6.80 (t, $CHNO_2$); 5.30 (m, OH)
7a	$(CD_3)_2CO$	—	—	3.41 s	—	—
7c	$CDCl_3$	—	—	3.32 s	—	—
7d	$CDCl_3$	—	—	—	8.10—7.30 m	—
8a	D_2O	—	—	3.60 s	—	—
10	$(CD_3)_2CO$	—	—	3.12 s	—	6.66 (s, CH_2)

Table 3. ^{13}C and ^{14}N NMR spectra of the compounds obtained

Compound	Solvent	^{13}C		^{14}N	
		CCl_2 or $O_2N—C—N$	Me or Ph	NO_2	=N→O
1e	$(CD_3)_2CO$	116.63	40.69 (Me—C); 37.33 (Me—S)	−1.63	−31.48
7c	$CDCl_3$	122.76	40.60 (Me—S)	−23.17	−45.97
7d	$CDCl_3$	122.64	135.69 (*p*-C); 129.73 (*m*-C); 129.16 (*o*-C)	−22.93	−46.13

1b. Found (%): C, 42.36; H, 4.64; N, 11.97; S, 9.50. $C_{12}H_{15}N_3O_7S$. Calculated (%): C, 41.74; H, 4.35; N, 12.17; S, 9.28. **1c**. Found (%): C, 32.27; H, 4.85; N, 13.90; S, 10.82. $C_8H_{15}N_3O_7S$. Calculated (%): C, 32.32; H, 5.05; N, 14.14; S, 10.77. **1d.** Found (%): C, 41.94; H, 4.69; S, 9.75. $C_{12}H_{15}N_3O_7S$. Calculated (%): C, 41.74; H, 4.35; S, 9.28. **1e.** Found (%): C, 22.74; H, 4.31; N, 19.29; S, 14.40. $C_4H_9N_3O_5S$. Calculated (%): C, 22.75; H, 4.27; N, 19.91; S, 15.17. **1g.** Found (%): C, 40.22; H, 4.18; N, 14.79; S, 12.40. $C_9H_{11}N_3O_5S$. Calculated (%): C, 39.56; H, 4.03; N, 15.38; S, 11.72.

General procedure for the synthesis of 2-(*R*-sulfonyl-*NNO*-azoxy)-2-nitro-1,3-propanediols (4a,b). Acetyl cloride (10 mL) was carefully added with stirring and cooling to a solution of compound **1** (10 mmol) in MeOH (100 mL). The mixture was boiled for 30 min and concentrated. Compounds **4** were isolated by column chromatography. **4a.** Found (%): C, 20.00; H, 3.90; N, 17.40; S, 13.10. $C_4H_9N_3O_5S$. Calculated (%): C, 19.75; H, 3.70; N, 17.50; S, 13.17. **4b.** Found (%): C, 35.67; H, 3.74; N, 13.67; S, 10.45. $C_9H_{11}N_3O_5S$. Calculated (%): C, 35.41; H, 3.61; N, 13.77; S, 10.49.

2-(Mesyl-*NNO*-azoxy)-2-nitro-di-*O*-nitro-1,3-propanediol (5). A solution of compound **4a** (1 mmol) in 70 % HNO_3 (20 mL) was heated for 1 h at 120 °C. The mixture was cooled, poured onto ice (100 g), and extracted with ether (3×50 mL). The extract was dried with $MgSO_4$ and concentrated. Compound **5** was isolated by TLC.

2-(Mesyl-*NNO*-azoxy)-2-nitroethanol (6). A solution of compound **4a** (5 mmol) in water (50 mL) was treated at ~20 °C with an aqueous solution of NaOH (15 mmol) and extracted with ethyl acetate. The aqueous layer was acidified with dilute HCl to pH 5—6 and extracted with ethyl acetate. The extract was dried with $MgSO_4$ and concentrated. Compound **6** was isolated by TLC.

General procedure for the synthesis of dihalo(sulfonylazoxy)nitromethanes (7). A solution of Na_2CO_3 (15 mmol) in a minimum amount of water was added to a solution of diol **4** (5 mmol) in 50 mL of water or 50 mL of a MeOH—water mixture (1 : 4), then Br_2 was added with stirring until the color no longer disappeared after the next portion was added (when Cl_2 was used, it was bubbled until the solution discolored; pH ~7 in both cases). The crystals that precipitated were filtered off. The oily products were extracted with chloroform and purified by TLC.

Potassium salts of bromonitro(sulfonylazoxy)methanes (8a,b). An equimolar amount of dibromide **7a,b** was added at 0 °C with stirring to a solution of KI (5 mmol) in a minimum amount of EtOH. The precipitated crystals of salts **8a,b** were

filtered off, washed with EtOH and ether, and dried in air. **8a.** Found (%): C, 7.61; H, 1.21; K, 12.27. $C_2H_3BrKN_3O_5S$. Calculated (%): C, 8.00; H, 1.00; K, 13.00.

Potassium salt of (mesyl-*NNO*-azoxy)nitromethane (9). A solution of compound **7a,b** or **8** (1 mmol) was refluxed for 1—2 h with KCN (3 mmol) in a minimum amount of ethanol and evaporated to dryness to give bright-orange crystals of compound **9**, which gradually deliquesced when stored in air.

A solution of compound **8** or **9** in a minimum amount of ethanol was diluted with an equal amount of water and treated with a threefold excess of Na_2CO_3, then Br_2 was added until the color no longer disappeared. The crystals of compound **7** that precipitated were filtered off. The compounds did not cause depression of the m.p. when mixed with authentic samples.

(Mesyl-*NNO*-azoxy)nitromethane (10). A solution of compound **7a** (5 mmol) and KCN (15 mmol) in ethanol (50 mL) was refluxed with stirring until discoloration (1—2 h), acidified at 5—10 °C with dilute HCl to pH 4—5, and concentrated. Compound **10** was isolated by TLC. Compound **10** was also obtained from salt **9** in a similar way.

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